Treatment of Hypertension

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Module

Cardiopulmonary module

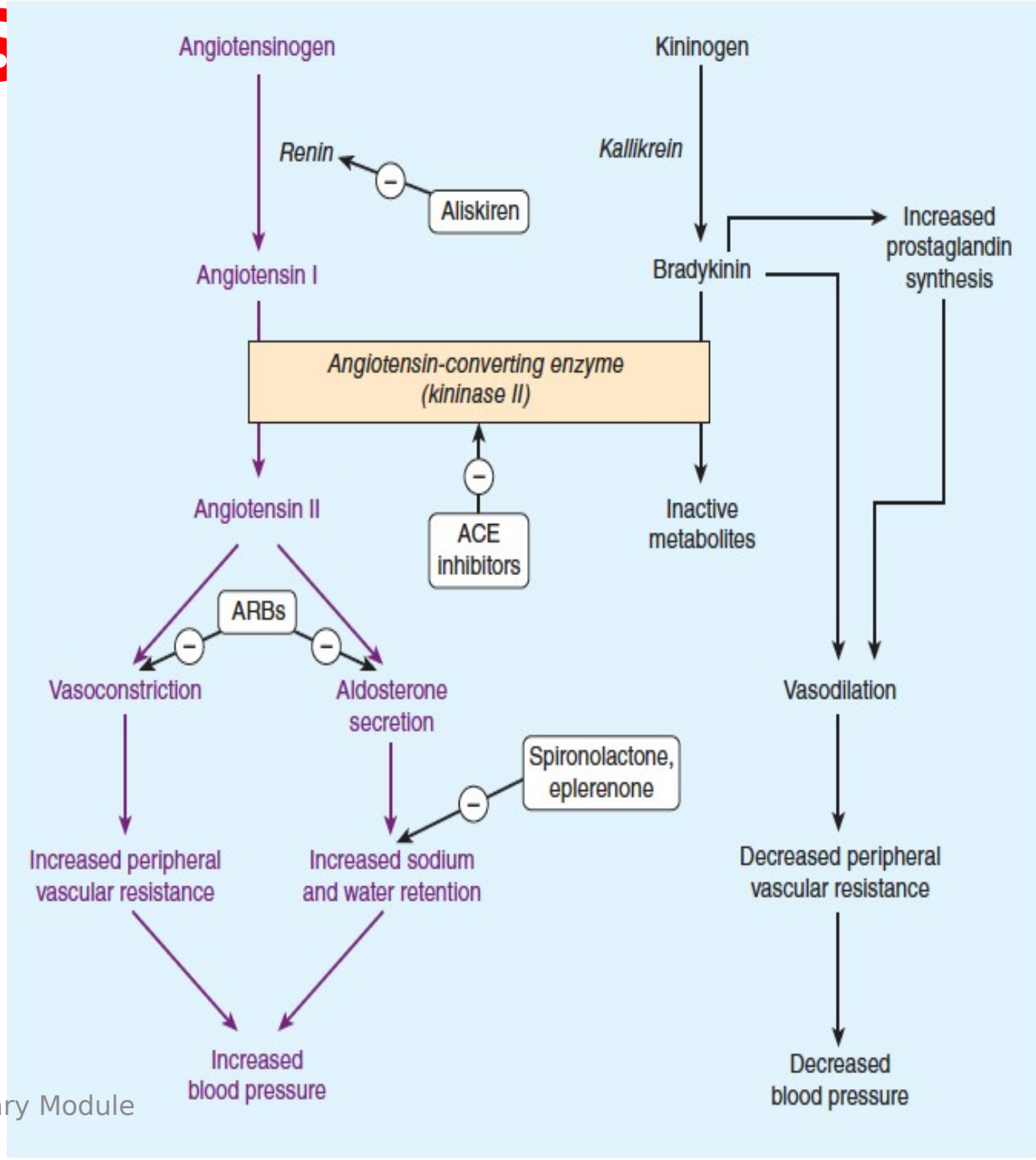
INTENDED LEARNING OBJECTIVES (ILO)

Lecture 2:

1. Explain the mechanism of action of anti-hypertensive drugs acting through the renin-angiotensin system
2. List the uses, adverse effects of ACEIs
3. Explain the role of calcium-channel blockers as antihypertensive drugs
4. Identify the 3 classes of calcium-channel blockers.

3. ACE INHIBITORS

- They **inhibit the converting enzyme peptidyl dipeptidase** that hydrolyzes angiotensin I to angiotensin II and (another name of the enzyme is plasma kininase).
- it also **inactivates bradykinin**, a potent vasodilator).
- The hypotensive activity of captopril results both from **an inhibitory action** on the renin-angiotensin system and a **stimulating action** on the kallikrein-kinin system.
- **They do not result in reflex sympathetic activation** and can be used safely in persons with ischemic heart disease.
- Cardiac output and heart rate **are not significantly changed.**



3- Angiotensin Converting Enzyme Inhibitors (

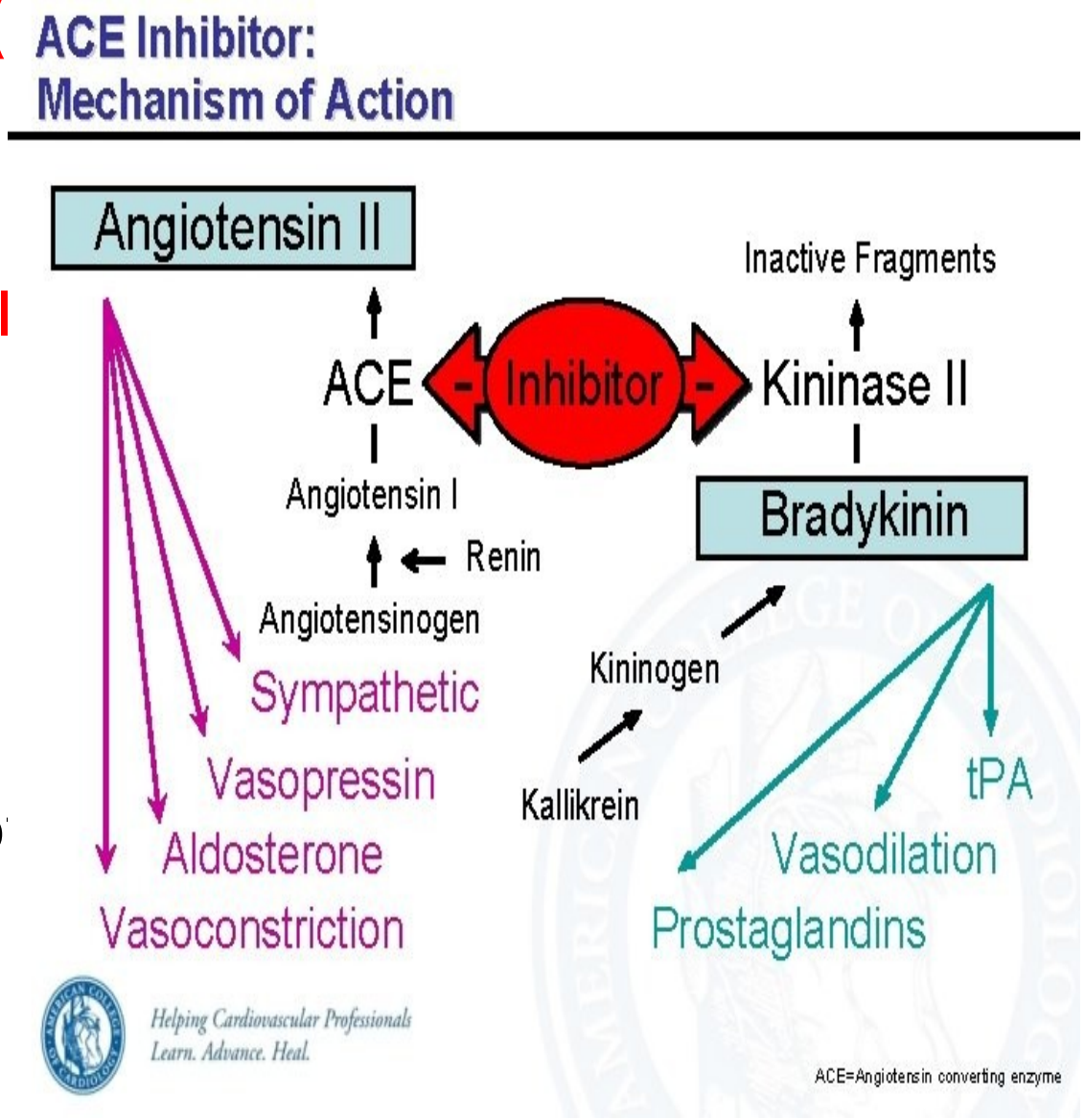
Mechanism of Action of ACEIs

Inhibit Angiotensin Converting Enzyme

1- Decrease conversion of inactive Angiotensin I to active Angiotensin II that results in:

a) Decrease VC.
b) Decrease Aldosterone (--Na + / fluid retention).
c) Inhibit Sympathetic activation.
d) Decrease Hypertrophy &Remodeling o heart & BV
e) Increase Renin & Angiotensin I.

2- Decrease Inactivation of Bradykinin (BK):



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Pharmacological Actions of ACEIs

a- **Mixed VD**: Arterio & Venous.

b- Arterio. VD decrease T.P.R.: decrease After-load & BP

c- Weak Vein. VD: decrease V.R. ,, decrease E.D.V. ,, decrease Pre-load & BP.

d- **C.O.P. is maintained**

e- Increase renal blood flow BUT decrease glomerular filtration rate (GFR) , (Efferent VD), decrease Glomerular hypertension.

f- Advantages:

- NO decrease of COP, even it may increase COP in HF.
- NO postural hypotension (Less Veno-dilator)
- NO reflex tachycardia (decrease Baroreceptors reflex & Sympathetic activity).
- NO abnormality in Glucose or Lipid or Cholesterol or Uric acid metabolism

Therapeutic Uses of ACEIs:

a- Hypertension, especially:

- High renin.
- Diabetic nephropathy because they diminish proteinuria and stabilize renal function (even in the absence of lowering of blood pressure). .

These benefits probably result from improved intrarenal hemodynamics, with decreased glomerular efferent arteriolar resistance and a resulting reduction of intraglomerular capillary pressure.

- Heart failure.
- But Not effective in Primary Hyperaldosteronism.

b- Heart Failure:

- Decrease both After & Preload: Improve cardiac performance and increase COP.
- Decrease Secondary hyperaldosteronism : Natriuretic : decrease edema.

Classification of ACEIs

1- S-H Containing ACEIs

Captopril

- Active drug.
- Well absorbed orally, *BUT* affected by food. Taken 1-2 hours before meal.
- Does not pass BBB.
- 50% metabolized in liver & 50% excreted unchanged in urine.
- Short acting. Used twice or thrice per day.
- Frequent side effects e.g. Angio-edema.

2- Non-S-H Containing ACEIs

- Less side effects than Captopril.
- Longer t1/2 , used once or twice per day.
- Oral absorption is not affected by meal.

A) Active Drugs:

Lisinopril: Active drug. NOT metabolized → Longest t1/2, used once daily..

B) Prodrugs

→ Metabolism → Active metabolites.

Enalapril → Enalaprilat **available ampoule for injection**

Perindopril → Perindoprilat

Benazepril → Benazeprilat

Ramipril → Ramiprilat

Quinapril

Fosinopril: **Excreted in bile**, not urine. Its dose has not to be readjusted in impaired renal function. As, Most of ACE inhibitors are eliminated primarily by the kidneys; **doses of these drugs should be reduced in patients with renal insufficiency**

Side Effects of ACEIs Contraindications of ACEIs

Cough

H.A.E = C1E Inhibitor Deficiency ↑ Bradykinin Levels

Angioedema → History of Angioedema/Anaphylaxis

Dry and irritant
Treat by NASID

Pregnancy Problems → Pregnancy

Fetal hypotension, renal failure, Oligohydramnios , Malformation

Taste Changes (Dysgeusia)

Other (Rash, Fatigue)

Proteinuria → B/L Renal Artery Stenosis

Renal Insufficiency → B/L Renal Artery Steno

Fatal Renal Failure.

Increased Potassium → Hyperkalemia

especially if accompanied with K+-retaining diuretics e.g.

Low Blood Pressure →

especially in Na+-depleted patients by diuretics.

Treat by Saline. Stop diuretics before the use of ACEI.

Drug Interactions of ACEIs

a- Na+-depleting diuretics accentuates the initial hypotensive effects.

b- K+-retaining diuretics e.g. Spironolactone augments the hyperkalemia effect.

c- NASID e.g. aspirin antagonize partially the hypotensive effect by blocking synthesis of PGs.

4. Angiotensin II (AT1) - Receptor Blockers

Members : Losartan, Valsartan, Candesartan, Telmisartan and Irbesartan

Non-peptide:

- **Compete with Angiotensin II for AT1-receptors.**
- **They are Pure antagonists.**

Pharmacologic effects of ARBs are similar to those of ACE inhibitors in that they produce:

a- Decrease V.C: V.D -They also release prostacyclin: VD.

b- Decrease Synthesis and release of Aldosterone

c-Inhibit Sympathetic activation: Block of presynaptic AT1-receptors on adrenergic neurons: decrease Noradrenaline release.

d-Prevent hypertrophy & Remodeling of Heart & BV due to hypertension.

a- VD of Renal vessels: decrease Glomerular hypertension (Efferent renal VD).

Metabolic Actions: correct side effects of diuretics Potassium retaining effect correct Hypokalemia.

Therapeutic Uses: Similar to ACEIs Effective orally.

Side Effects: Similar to ACEIs BUT **although the risks of cough and angioedema are significantly decreased.**

5. Renin Inhibitor

I. ↓ release:

- A selective renin inhibitor, aliskiren
- Aliskiren directly inhibits renin and, thus, acts earlier in the renin-angiotensin-aldosterone system than do ACE inhibitors or ARBs. **As it blocks the rate-limiting step of the renin–angiotensin– aldosterone system (RAAS).**
- It lowers blood pressure about as effectively as ARBs, ACE inhibitors, and thiazides.
- Aliskiren can also cause cough and angioedema but probably less often than ACE inhibitors.
- Aliskiren is contraindicated in pregnancy.
- Aliskiren should be prescribed with caution for patients with moderate renal dysfunction.

II. Renin receptor blockers:

- e.g enalkiren, remikiren

6. Calcium-Channel Blockers

Classes

- The calcium-channel blockers are divided into three chemical classes

1. Diphenylalkylamines:

- ***Verapamil***
  - Has effects on both cardiac and vascular smooth muscle cells.
  - Its effect on the heart is more pronounced than its effect on blood vessels.
  - It inhibits cardiac properties and so produces bradycardia and it produces weak V.D.
  - Due to inhibition of cardiac properties, it is used to treat arrhythmias.

2. Dihydropyridines:

- ***Nifedipine: amlodipine,*** *felodipine, isradipine, nicardipine, and nisoldipine.*
- Affects vascular smooth muscle more than the cardiac muscle.
- Cause vasodilatation with minimal effect on the heart.
- Reflex sympathetic activation with slight tachycardia maintains or increases cardiac output in most patients given dihydropyridines.

3. Benzothiazepines:

- ***Diltiazem:***
  - Affects both cardiac & vascular smooth muscle equally.
  - Causing negative inotropic effect and V.D.

Therapeutic uses of calcium-channel blockers:

- These agents are useful in the treatment of hypertensive patients who also have
  - asthma,
  - diabetes, OR
  - angina.

Adverse effects and contraindications of calcium channel blockers

1. Dizziness, headache, and a feeling of fatigue
2. *Verapamil should be avoided in patients with congestive* heart failure or with atrio-ventricular block due to its negative inotropic and dromotropic effects.
3. *Nifedipine has caused gingival enlargement.*

Mention THREE adverse effects of **ACE inhibitors.**

Mention 3 classes ca channel blockers

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Neal L. Benowitz, MD. In: Katzung BG (ed.). (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.